Dr. David Stukus: Hello and welcome to "Conversations from the World of Allergy", a podcast produced by the American Academy of Allergy, Asthma, and Immunology. I'm your host, Dave Stukus. I'm a board-certified allergist and immunologist and serve as the social media medical editor for the Academy. Our podcast series will use different formats to interview thought leaders from the world of allergy and immunology. This podcast is not intended to provide any individual medical advice to our listeners. We do hope that our conversations provide evidence-based information. Any questions pertaining to one's own health should always be discussed with their personal physician. The Find an Allergist http://allergist.aaaai.org/find/ search engine on the academy website is a useful tool to locate a listing of board-certified allergists in your area. Finally, use of this audio program is subject to the American Academy of Allergy, Asthma, & Immunology terms of use agreement which you can find at http://www.AAAAI.org. Today's edition of our "Conversations from the World of Allergy" podcast series has been accredited for continuing medical education credit. The American Academy of Allergy, Asthma, and Immunology is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. Information about credit claiming for this and other episodes can be found at https://education.aaaai.org/podcasts/podcasts. Credit claiming will be available for one year from the episode's original release date. Today we are pleased to welcome Dr. Tom Casale, who will discuss the use of biologic therapies for treatment of asthma. Dr. Casale is a professor of medicine in the Division of Allergy and Immunology at the University of South Florida Health Morsani College of Medicine. Dr. Casale has had a long and distinguished career with over 300 peer-reviewed publications and extensive pioneering research investigating asthma pathogenesis, phenotypes, and novel treatment options. Dr. Casale has held numerous leadership positions throughout his career, including as past president and executive vice president of the academy. Dr. Casale's latest pursuits include his current role as the chief medical advisor for operations for FARE. I do not have any relevant relationships to disclose. Dr. Casale serves on the advisory boards of Sanofi-Regeneron, Novartis, Genentech, and Astrazeneca. He also serves as a speaker on asthma pathogenesis for Thermo Fisher and as an advisory board member for Genentech. Dr. Casale, thank you so much for taking the time to join us today and welcome to our show.

Dr. Tom Casale: Thanks, Dave. It's a pleasure to be here.

Dr. David Stukus: Well, great. We're going to have a great discussion today surrounding biologics. But before we get into some of the details, can you orient our listeners and help explain what the term "biologics" actually means?

Dr. Tom Casale: Sure. So, a biologic or biologic drug is really a product that's produced from living organisms or, at least, contain components of living organisms. So, there's a wide variety of them. For example, they could be vaccines, blood components, etcetera. In the case of allergy and asthma, most

biologics have been considered to be those things that are monoclonal antibodies and used for the treatment of various disorders.

Dr. David Stukus: And how would biologics differ from other types of medications? For instance, inhaled corticosteroids that we use to treat asthma?

Dr. Tom Casale: Again, I think the biggest difference, again, is the biologic is produced from a living organism, whereas an inhaled corticosteroid or a leukotriene modifier, or whatever drugs that you're talking about, are really synthesized without using a living organism. So, it's different in that respect. And I think also the biologics are often times referred to as biologic response modifiers; because of the way they work, they change the operation of a natural biologic intracellular or cellular action. So, if we have a biologic against interleukin-5, we're really talking about a monoclonal antibody that affects that particular molecule.

Dr. David Stukus: And, so, if we talk about targeted therapies with biologics for asthma and allergic conditions, what are the immunologic pathways that are most important for these treatment options?

Dr. Tom Casale: Well, when we're talking about asthma, we've divided asthma up into two very big phenotypes; that is, those that involve patients that have what we call T-2 low inflammation, or inflammation that's primarily mediated by neutrophils. In that case, when we look at the mediators and cytokines that we thought are going to be important, we think about things like interleukin-8, interleukin-17, TSLP, IL-6-- molecules like that that are capable of driving neutrophils to the site of inflammation and activating those neutrophils to produce a number of the biologic effects that we see in patients with asthma. The other big phenotype that we see in asthma is what we call Type 2 high inflammation and these are patients that, by and large, typically have an eosinophilic-predominant inflammation. The molecules that are thought to be most important for Type 2 inflammation include IL-4, IL-13, IL-5. But there's overlap, because TSLP and the IL-33 and IL-25, although important for the Type 2 low inflammation, also play a role in the Type 2 high inflammation. And then, finally, I think another pathway that we think might be important in this Type 2 high inflammation is mediated by PGD-2 and that works through stimulation of what we call DP-2 receptors, which are present on a number of inflammatory cells.

Dr. David Stukus: So, that's really a lot of different types of signaling molecules. And it sounds like they ultimately have some overlap, but, yet, have various pathways to create a different end result that can promote inflammation. Do you think that's sort of an accurate summary?

Dr. Tom Casale: I do. And it's important to recognize when we say somebody has got Type 2 high inflammation and we expect to see a lot of eosinophils in these patients. That does not mean that they don't have neutrophils; they do typically, but the eosinophil tends to be the predominant cell. And the same with the Type 2 low inflammation: Predominantly neutrophils, but they may very well have some eosinophils that are important.

Dr. David Stukus: And we're going to talk very soon about the differences and how to identify these T-2 low- and T-2 high-type of asthmatic patients. But before we get there, for most individual patients do they

generally stick with one pathway or the other throughout their life or do you see people actually switching from one type to another?

Dr. Tom Casale: That's a good question and I think if you have a certain type of genetic predisposition--for example, if you have that genetic predisposition to be allergic, you are most likely going to have that T-2 high inflammation. And if you develop asthma later in life as an adult, you may or may not have that T-2 high inflammation and pattern. So, a lot of patients that develop asthma later in life can be eosinophilic, but not allergic; or they could be more neutrophilic. That's different than in the younger age range where allergies tend to be much more common. So, it's unusual to see a child, for example, that would have a Type 2 low inflammation. They tend to have more atopy and more of a T-2 high-driven inflammation. Now, as they progress through life, however, they could change that phenotype depending upon what happens. And a typical example would be you could have an allergic child who looks like they're Type 2 high, but, because of an occupational exposure, could develop a Type 2 low type of asthma where neutrophils are important. So, in general, people tend to stay the same, but there are instances where they can change.

Dr. David Stukus: Oh, thank you. That's fascinating. And I think the heterogeneity of asthma overall is just extremely fascinating and our understanding that has grown over the last couple of decades. And can you just touch upon some of the shared characteristics of asthma as well as ways in which it can differ among patients? Because not all asthma is the same.

Dr. Tom Casale: That's true. And I don't-- and when we think about it, we have patients that, for example, just have asthma-like symptoms or asthma when they exercise or when they're exposed to cold air, and we have asthma patients that have very mild disease that occasionally will have some wheezing or shortness of breath; and they're much different than what we see in a specialty clinic where we'll have very severe disease with symptoms on a daily basis, corticosteroid dependency. Now, we have not been able to discern how you could differentiate those two based on characteristics from looking at their lung tissue, for example. If you take patients that have fairly mild disease, they may have a high degree of inflammation or they may have what we call airway remodeling changes with increased smooth muscle mass, etcetera, but they don't have any symptoms. And we're not exactly sure why that is. It could be in part due to a perception of dyspnea. It could be in part through neural immune mechanisms, but there's clearly differences, but also similarities, across the range of asthma.

Dr. David Stukus: And you mentioned that the tissue level may be difficult to sort of determine some of these things, but what are some of the clues that physicians can use to determine what type of asthma somebody has? Are there parts of the clinical history that are more important than others, or are there any tests that may help?

Dr. Tom Casale: Yeah, I think the history is going to be very important. So, obviously, the first thing that you have to do is to make sure does the patient have asthma. So, do they have the typical symptoms of shortness of breath, wheezing, cough, and those symptoms brought on by triggers that we typically see with asthma as a manifestation of what we call airway hyper-responsiveness. And those triggers would be things like exercise or cold air or changes in temperature or humidity that are somewhat rapid. Those

would all be things that we would look for. In addition, we would like to see if a patient has typical airway changes manifested by their physiologic measurements on spirometry. Do they have a decrease in FEV1? Do they have a decrease in the FVC? And what is the ratio of the FEV1-FVC? Do they have a response to bronchodilator? The ATS criteria for defining those physiologic changes include a 12 percent increase in FEV1 and 200 milliliters after bronchodilator therapy. But we know that not all patients have that and that's a variable component, where you may have it one day, but you not see it the next day. That may be due to underlying, severe inflammation or other factors. And then, finally, we look at perhaps another biomarker and that's exhaled nitric oxide. If it's high-- and by high we typically mean greater than 25 or more-- then we start thinking about does this patient have underlying airway inflammation typical of asthma? So, we look at symptoms, we look at spirometry values, and we look at exhaled nitric oxide, excluding factors that can be confused with asthma, making sure the patient isn't wheezing, because they have COPD or congestive heart failure or another cause.

Dr. David Stukus: And if we're trying to determine more eosinophil-driven, or T-2 high, versus neutrophil-driven T-2 low, are there certain co-morbid conditions that would help sort of sway that decision one way or the other?

Dr. Tom Casale: Yeah, so, you're more likely to have a T-2 asthma, again, if you're someone who had atopic conditions at your childhood or even into adulthood. So, if you have food allergies or atopic dermatitis or allergic rhinitis, you're much more likely to have allergic asthma in a T-2 high type of phenotype. However, again, if you develop asthma later in life and you don't have any of those atopic predispositions, then you would be perhaps more likely to have a T-2 low asthma. Or if you're one of the individuals that have asthma and smoke cigarettes, unfortunately we see that the U.S. statistics for smoking cigarettes, although dropped in the general population, is actually a little bit higher in patients with asthma than the general population and approaches 20 to 21 percent. Those patients tend to have more of a neutrophil-driven disease. It's important to know that, because as we'll probably talk later, the treatment options are going to be different. And the effectiveness of those treatment will be different as well.

Dr. David Stukus: So, it sounds to me like this is a very complicated sort of decision tree that comes into play in regards to the types of symptoms and making sure you establish the diagnosis of asthma in the first place and then really working through the different types of phenotypes and factors that may be kind of underlying that asthma. You mentioned that the response to treatment can vary as well. What's the typical progression of treatment options for patients when they have poorly controlled or persistent asthma and then as the follow-up to that, when should we start thinking about biologics? And what's the optimal patient?

Dr. Tom Casale: Yeah, so, I think the one thing to remember is not everybody responds to every drug. So, even though if we look at how we treat asthma, the single drug that's used in almost every step is inhaled corticosteroid. But we know that every patient will not respond to corticosteroids and if you look at the overall responsiveness to patients with asthma it's a bell-shaped curve as it is with any drug for any disease. But there are certain features that we know would predict a higher likelihood of response to inhaled corticosteroids which are recommended for Step 1 through Step 5 treatment of asthma. That is

patients that have mild persistent to severe persistent asthma. The patients that smoke cigarettes, for example, are not going to respond to inhaled corticosteroids very well. Obese patients tend to respond less well than non-obese patients. So, these types of decision-making pieces of information need to be in the back of your mind as you start looking at the recommended therapies for patients with asthma, which in the very mild case is usually a low-dose inhaled corticosteroid; the next step would typically be to increase that dose, plus or minus the addition of a long-acting beta agonist. And then if no response and the patient is still symptomatic as asthma exacerbations, you start thinking about other drugs like tiotropium, which is an anticholinergic agent, and that's been shown to work in patients regardless of the T-2 phenotype, as well as leukotriene receptor antagonists, especially if they have features that are more likely to respond to those drugs and that would be patients that have asthma-exacerbated respiratory disease or perhaps or perhaps nasal polyposis. And there's some literature to suggest that they may be a better option, for example, in patients that are obese. And once you get into patients that aren't responding very well to a medium or high dose inhaled corticosteroid, plus a long-acting beta antagonist and they have failed the addition of tiotropium or leukotriene receptor antagonist, these are the patients that we would consider as candidates for biologics. And right now we have five different biologics to choose from. The choice will be governed by a lot of different things, including the specific characteristics of the patients.

Dr. David Stukus: So, it sounds like really-- if following a step-wise approach to therapy, the patients who should be considered for biologics really are going to declare themselves as being poor responders to the current standardized management and, as you mentioned, higher level therapy.

Dr. Tom Casale: Right. And these are patients also that typically would have relatively frequent exacerbations, at least one or two times a year. That we would consider for a biologic.

Dr. David Stukus: Okay, thank you for clarifying that as well. I think that's a key component to consider. Now you mentioned five currently available biologic treatment options for asthma. Can you briefly describe what those are and what they target?

Dr. Tom Casale: Sure. So, the first one that has been on the market for over 15 years now is omalizumab, which is an anti-IgE monoclonal antibody. And this drug is dosed based on body weight and IgE level. It would be an agent that you would consider for patients that have a strong allergic component. The next category of drugs are those that block the IL-5 pathway and interleukin-5 is very important for eosinophil growth and differentiation. So, IL-5 blockers, there are three on the market. Two, reslizumab and mepolizumab, target IL-5 itself. The other one is benralizumab and benralizumab binds to the IL-5 R-alpha receptor. So, it binds to the receptor, which is present on eosinophils and basophils and actually causes antibody dependence cell-mediated cytotoxicity, so that those cells that have IL-5 R-alpha on their surface that have IL-5 monoclonal antibody benralizumab bound to that are prone towards cell death. The other biologic, which is entirely different in regards to the pathway it works on, is the monoclonal antibody dupilumab and dupilumab works by effecting the IL-4 and IL-13 pathways, because it binds to the common alpha chain for signaling for those two cytokines, interleukins 4 and 13. It binds with the IL-4 alpha receptor and prevents the IL-4 or IL-13 from acting on that cell causing downstream effects. And in

the case of interleukin-4 that's important for switching from making IgM to IgE, among other things; and IL-13 is important for a number of different things including airway hyper-responsiveness.

Dr. David Stukus: That was a fantastic summary. You know, I just thought of a question that's been asked from me and I'd like to hear your response to this: We know with omalizumab dosing-- and we're going to talk about selecting different biologics that a total IgE level is useful. Is there any indication to obtain a level of interleukin-5, interleukin-4, interleukin-13 prior to consideration of these biologic agents?

Dr. Tom Casale: Yeah, so, for-- let me just back up just one second. So, we do get an IgE level for omalizumab. I want to make the point that IgE is not a very good biomarker for disease. But it's important for dosing omalizumab. And a number of years ago, we showed that unless you knock down that IgE to a very low level, patients didn't have a very good clinical effect. In the case of the IL-5 blockers, do people respond better if they have elevated IL-5 levels? The answer is yes, but that's mostly been shown in sputum samples, so something that we're not going to get for point-of-care tests. And that's the same with IL-4 and IL-13, where as far as a point-of-care test we don't have one with the exception of exhaled nitric oxide. Now why do I bring that up? It turns out that interleukin-13 stimulates the airway epithelium to make exhaled-- to make nitric oxide, which you can measure. When you look at a drug like dupilumab you actually have a biomarker that's somewhat more specific because it targets a-- or results from a target of dupilumab, and that is IL-13. So I don't know if that completely answers your questions, but that's the way we're tending to think right now, is that we don't have extremely specific biomarkers for individual drugs. We tend to measure things that are point-of-care, like blood eosinophil levels for exhaled nitric oxide. What we're really lacking is a biomarker that you could say, "Tom, which is these drugs would you definitively pick for a patient?" There's a big overlap, and I'd be happy to discuss that in more detail if you want.

Dr. David Stukus: No, absolutely. I think we're going to get to that after just a couple of questions. And yes, thank you, you absolutely answered my question. I see why people would ask that, and it makes sense if we're targeting specific molecules to actually think about do we measure them firsthand. So now I have a great answer next time I get the question, so, thanks. Briefly, how are biologics administered? Is this something that people take orally? Is it intramuscular? Is it subcutaneous?

Dr. Tom Casale: So right now all of the biologics that are approved, with the exception of reslizumab, are delivered subcutaneously, but the difference is the dose in frequency and also whether they're home-based administration or not. So in the case of anti-IgE, it's a subcutaneous injection or two injections, based on body strength and IgE, that's every two to four weeks. In the case of mepolizumab, it's a monthly subcutaneous injection. Benralizumab is a monthly subcutaneous injection for the first three months and then it's every two months, and in the case of reslizumab, it's actually weight-based dosing that's delivered intravenously. And then finally dupilumab is every two weeks, but that's self-administered, at home, subcutaneously. So there are differences, and this is when we use that concept of shared decision-making when you're talking with your patients and there isn't a good discrimination between, "Gee, which of these do I want to use?" If you can't come up with a good discriminating factor on picking one over another, it's important to ask your patients which one they're more likely to use. Some patients don't want to come to the doctor every two to four weeks, so they would be perhaps a better candidate for

a drug that's self-administered. Some people are very obese and they might do better with weight-based dosing, so perhaps a drug that's administered intravenously like reslizumab might be better. Others, coming in every eight weeks is not a big deal, so perhaps benralizumab. But those types of things ought to be presented to the patient so they could help make the decision so that it would hopefully increase their adherence to the program.

Dr. David Stukus: Those are great points. The magic question is always going to be, "What's the point?" So can you talk about the expected outcome from using biologics? Every patient wants to know how soon after starting are they going to feel better. Can you comment on that as well?

Dr. Tom Casale: So I think it's very important to identify what you're trying to do with that biologic. Why are you treating a given patient with a biologic? If it's to reduce asthma exacerbations and your patient has two exacerbations per year, it's going to take a while perhaps to see a difference, because if you cut the number of exacerbations by 50 percent, which in broad strokes all these biologics do, you won't know that perhaps for a long time. However, if you're trying to improve lung functions or you're trying to improve symptoms, you may see those effects much more quickly depending upon the biologic that you pick. So an example would be dupilumab. Dupilumab has been showed to increase FEV1 within two to three weeks. So there's an indication, if you have a patient that you're trying to increase FEV1 and you see that increase, then you know the drug is probably active and doing what you're hoping to do. So a lot of it depends upon what you're trying to achieve with that drug, but in general most people would say, "Give it a chance for about four to six months before you make a decision-- it didn't work, or I'm going to try a different biologic."

Dr. David Stukus: Do you generally recommend having a conversation with the patient of what objective measure is going to be utilized as well as the time period at the start of treatment? Is that something that's helpful?

Dr. Tom Casale: It is helpful for some patients. I think if you take a drug like omalizumab, it typically does not improve pulmonary functions by a lot. Now, there's exceptions to every rule, but it does improve ACT scores; it does improve symptoms; and it reduces exacerbation. So there's a case where I would say, "Look, okay, your ACT score is below 19, you're not well controlled," say it's 14, "Let's follow your ACT score and see whether or not you improve, along with spirometry and whether we prevented exacerbations." Showing people what you're trying to achieve with these biologics in some sort of fashion I think helps them be more engaged in being adherent to the therapy and justifying for a lot of patients the extra cost and the extra time it takes them to perhaps come into the doctor every two to four weeks to get their injection.

Dr. David Stukus: Those are very important things to consider, absolutely. The other thing that raises concern, as it should, would be any adverse effects. Can you mention the major concerns with the different biologic therapies in regards to the adverse effects that have been discovered?

Dr. Tom Casale: Yeah, I'd say that overall the type two high biologics have been relative safe as far as adverse event profile. So that's good news. I'll get back to that in a second, but I wanted to make a point

that the patients with the type two low asthma that are more neutrophil driven, there's where we've had some difficulties in trying to block those pathways and not see perhaps adverse events that are bothersome. So when attempts were made to block TNF-alpha in certain patients, they developed malignancies or infections that were problematic. And you have to think about the fact that if you're really trying to prevent that neutrophil from getting into the airways, yeah, I might be able to help your asthma, but am I going to predispose you on toward consequences like increasing pneumonias or other problems? With the T2 high biologics, we're targeting cytokines or cells that have not been shown to be a major issue as far as if I take them out, a patient could expect to have an untoward adverse event. So they've had relative good side-effects. Omalizumab, the incidence of anaphylaxis has been the biggest thing, and that occurs in about 0.1 to 0.2 percent of patients. We still don't know the mechanism, but it's something that you should be aware of, and that's why we tell patients, "For the first three doses, we want you to wait in the clinic for two hours, and thereafter 30 minutes." The reason for that is if you look back historically, you would capture about 75 percent of the episodes of anaphylaxis, so they would be treated in clinic, which makes sense. If you look at IL-5 blockers-- we'll start with mepolizumab-- they really haven't had a big problem other than with mepolizumab there is a concern about pre-vaccinating with herpes zoster vaccines. When you look at benralizumab, there's a concern that patients do, about 10 to 15 percent of the time, develop neutralizing antibodies to the benralizumab, but that has not been shown to affect the efficacy or safety thus far. When you look at reslizumab, you do have a few patients that also develop anaphylaxis. And then finally, when you look at dupilumab, the two things that have really popped up more with that drug is you tend to get an increase in blood eosinophil levels to start with. So in patients that start out with really high blood eosinophil levels, there's a concern about raising them even higher. The other thing that's been shown with dupilumab is problems with conjunctivitis. That's been rarely reported in patients treated with asthma, more common to see that in patients with atopic dermatitis treated with dupilumab.

Dr. David Stukus: You talked a lot about the variability with asthma, and you also mentioned sort of committing to a four- to six-month treatment duration before deciding to proceed more long-term. Are we at a point where we can use some of these biologics more on an as-needed basis, if there's variable asthma exacerbations during times of the year, or really are they best utilized consistently for prolonged periods of time?

Dr. Tom Casale: That's an excellent question. I personally think we need to do more of those types of studies, because I believe that certain of these agents could be used more on an as-needed schedule. So a great example would be omalizumab. If you look at the data with omalizumab in children, published in New England Journal, the ICATA study, what they found is that the seasonal increases in asthma exacerbation is primarily due to viral infections were prevented by the use of omalizumab, and it's subsequently been shown that in patients that are atopic-- if their dendritic cells have allergen bound to the high-affinity IgE receptor through IgE, on the dendritic cell, they have a deficiency in their ability to produce interferons in response to viral infections. Omalizumab decreases IgE, and as a consequence decreases the high-affinity IgE receptor and actually restores the ability of the dendritic cell to produce interferons that are important for viral infections. So long story short, you could conceivably say, "Look, I have kids or adults that typically get these exacerbations every fall when they go back to school, or their kids go back to school, and they get viral infections. What if I give you a couple of doses of omalizumab?

Can I prevent you from having that exacerbation?" I think these are the types of things we have to think about, because I do believe that there's a role for these drugs on an as-needed basis. Another good example would be benralizumab, where there was a study published a few years ago where they gave benralizumab in the emergency room for patients that had an acute exacerbation, and what they found is they markedly decreased the recurrence of exacerbations over six months with just a single injection. So I think there's room for considering different paradigms for the treatment with these biologics.

Dr. David Stukus: That is truly fascinating. With any luck and some additional research, hopefully we can revisit that on a future podcast. That'd be great. Now, the moment has come. I think that this has been a great sort of background and discussion in regards to the differences in asthma and the biologics that are currently approved as well as the pathways that they target. Can you offer some pointers and some advice in regards to how physicians and allergists can really decide which biologic to use for which patient? What can they start with, and how can they proceed from there?

Dr. Tom Casale: So, first off, you want to assure yourself that the patient really has a T2 high profile, because the five biologics that are approved are for those types of patients; and then you have a decision between the five. If you look at the GINA 2019 update on the asthma guidelines, they have some basic parameters that they recommend, and I think by and large they're fairly accurate. So what they say is if you have type two airway inflammation and you have blood eosinophil levels or exhaled nitric oxide that are high, and in the case of type two asthma-- they define it as a blood eosinophil level greater than 150; others may define it greater than 300; an exhaled nitric oxide greater than 20; others might use 25 as a cutoff-- then you would probably fit into that type two paradigm. Which one do you pick? Well, if you have sensitization on prick-skin testing or allergen-specific IgE to perennial allergens that you think are clinically relevant for that patient, and that patient fits within the weight and IgE dosing range, recommendation would be probably start them with anti-IgE. If the patient has either no A-to-P [ph?] or you don't think it's a big contributor and they have elevated blood eosinophil levels, then in the case of the IL-5 blockers-- what's been shown is that the higher the blood eosinophil level the greater the responsiveness-- they might be a better candidate for an IL-5 blocker. And then those patients that have eosinophilic asthma, we have elevated exhaled nitric oxide, and those patients typically respond best to the IL-4 or 13 blocker dupilumab. So those are some general guidelines. They'll still overlap because, as I said, we don't have specific biomarkers to tell me, "That's the drug to use for that patient." They all work better in patients with higher blood eosinophils, so that's a little bit hard to separate them out based just purely on eosinophil levels.

Dr. David Stukus: What about the patient who doesn't have allergic sensitization and they have no evidence of elevated peripheral eosinophilia or increase in exhaled nitric oxide? Do those patients exist? And if so, should we consider biologics for them at all?

Dr. Tom Casale: They really do exist, and that probably makes up about 25 to 40 percent of patients with asthma, and at this point none of the biologics that we currently have shown really good response profiles in those patients. So we're waiting for drugs that work in patients that fit that paradigm. Some of the candidates that we might see-- tezepelumab, which blocks TSLP. At least in the Phase 2 data, it appeared to work equally well in patients whether they had high or low blood eosinophil levels, but we

have to see what happens in the Phase 3 studies. And then there are several ongoing studies to look at other potential molecules that could be important in those patients; IL-17 blockers, IL-6 blockers are examples of a couple.

Dr. David Stukus: If I may summarize for a second, I'm hearing from you that asthma by definition is a very heterogeneous condition that's hallmarked by various inflammatory mediators that can take on different pathways, whether it's T2 low or T2 high, and in consideration of treatment options, we really need to think through a lot of the details that can help us determine which pathway they're on, and then furthermore, in consideration of biologics, we really need to be thoughtful about what may be driving their underlying asthma as far as what we're going to target with treatment. Did I miss anything?

Dr. Tom Casale: Yep, except one more thing that I would add, and that would be the presence of comorbid conditions that have been shown to respond to one of the biologics that you would typically use for asthma. I think when you look at patients that have atopic dermatitis, you might very well pick dupilumab because that is a drug that's approved for atopic dermatitis. So if they have both, they might do well. If you have a patient with nasal polyposis, none of them have been approved for nasal polyps, but the press release on the Phase 3 data for dupilumab was very positive, and omalizumab, mepolizumab and benralizumab are in Phase 3 trials, so they might be agents that you would consider down the line. If they have food allergy, omalizumab and perhaps dupilumab. If they have allergic rhinitis, clearly omalizumab, but dupilumab also has some positive data in that regard. So I think it's important to keep those things in mind as well.

Dr. David Stukus: Great. This podcast has been amazing. I can't thank you enough for joining us, and this has been a wonderful discussion, but it's a lot to take in. You mentioned the GINA 2019 guidelines and their website. Are there any other resources that are available to help providers and patients understand the different options?

Dr. Tom Casale: Yeah, unfortunately the NIH guidelines are very outdated, so you're not going to find it there, but both of our journals, JACI and JACI: In Practice are good resources to look at reviews that are fairly current on the biologics, and in fact JACI: In Practice just had a whole issue on biologics, and there's a lot of good information there about treating patients not only with asthma but also considering the use of biologics down the line for COPD.

Dr. David Stukus: Great. We can put that for our listeners who want to obtain CME credit-- we'll put those links on the website as well. Lastly, today was all about asthma and use of biologics, but can you briefly mention what other allergic conditions biologics are currently approved to treat and then thoughts on future prospects?

Dr. Tom Casale: Sure. So as I mentioned, if you're thinking about using a biologic for asthma, think about the comorbid conditions. But right now we have dupilumab, which is available for the treatment of atopic dermatitis. We have omalizumab, which is available for the treatment of chronic urticaria, and I think it's made a huge difference in patients that have urticaria. Mepolizumab is approved for EGPA, which is eosinophilic granulomatosis with polyangiitis, but outside of that, none of the biologics are approved for

anything else. In the very near future I would expect that you'll see several of these approved for nasal polyps and probably omalizumab and perhaps dupilumab for food allergy, and if you look at other indications, it gets a little bit murkier. We don't know if any of these biologics will have a big role in COPD. Most of the trials with the T2 biologics have shown a statistically scientific reduction in exacerbations with them, but it's been a relatively low effect, like about 20 percent reduction, as opposed to what we see in asthma, which tends to be 50-plus percent.

Dr. David Stukus: So it sounds like stay tuned for that as well. That's great. Dr. Casale, I can't thank you enough for taking time out of your busy schedule to be with us today. I think that this was an extremely helpful conversation. Before we say goodbye, is there anything else you'd like to add?

Dr. Tom Casale: Well, I think the only thing I would add is it's very exciting to think about all these different biologics, but none of them thus far as induced what we would call true immunomodulation. So we need drugs that not only block those pathways but change the immune system in a way that you could treat a patient for a finite time, stop the drug, and they have long-lasting remission of their symptoms. That's lacking, and that's what we hope to have in the future.

Dr. David Stukus: Great. Thank you again.

Dr. Tom Casale: Thank you, Dave. My pleasure.

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